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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,044	07/21/2003	Andrew J. Murphy	REG 780BZ	6377

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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,044	MURPHY ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-52* is/are pending in the application.

4a) Of the above claim(s) *40-43 and 48-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-39 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7212003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment received on 7/21/2003 has been entered. Claims 1-34 have been cancelled. New claims 35-52 have been added. Claims 35-52 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 35-39, 44-47 and 52, drawn to a non-human organism, particularly a mouse, comprising a genetically modified immunoglobulin variable gene locus, classified in classes 800 and 800, subclasses 13 and 18.

II. Claim 40, drawn to a genetically modified immunoglobulin variable region gene locus, classified in class 536, subclass 23.1.

III. Claims 41-43, drawn to an antibody, classified in class 530, subclass 387.1.

IV. Claims 48-51, drawn to a method of making an antibody, classified in class 435, subclass 70.21.

Inventions I-III are patentably distinct each from the other. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are products that have separate uses and have different modes of operation. The products of Groups I-III, each from the other, have

different structures and can be used in materially different methods that have different technical considerations. For example, the non-human organism of Group I can be used in a screening assay for identifying agents that bind an immunoglobulin, the gene locus of Group II can be used as a probe in a hybridization assay *in vitro* and the antibody of Group III can be used to detect an antigen in a cell *in vitro*. Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and separate search requirement, restriction for examination purposes as indicated is proper.

Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the method of Group IV can be practiced with a different non-human animal while the non-human organism of Group IV can be used to screen for agents that bind an antibody. Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and separate search requirement, restriction for examination purposes as indicated is proper.

Inventions II and IV are patentably distinct Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different

designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions have separate uses, different structures and different functions. For example, the gene locus of Group II could be used as a probe in a hybridization assay in vitro while the method of Group IV could be used to produce an antibody. Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and separate search requirement, restriction for examination purposes as indicated is proper.

Inventions III and IV are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the antibody of Group III could be made by another process. For example, the antibody could simply be isolated from the mouse after antigenic stimulation. Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and separate search requirement, restriction for examination purposes as indicated is proper.

During a telephone, conversation with Valetta Gregg on 1/17/06 a provisional election was made without traverse to prosecute the invention of Group I, claims 35-39, 44-47 and 52.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 40-43 and 48-51 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

The priority claim as submitted in the preliminary amendment received on 7/21/2003 should be updated to include the patent number of allowed application 09/784,859.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For example, see pages 27 and 37 as well as throughout the entire specification. All embedded hyperlinks must be deleted.

Appropriate correction is required.

Claim Objections

Claim 52 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot refer to two different products from two different claims. See MPEP § 608.01(n). Accordingly, the claim 52 not been further treated on the merits.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-39 and 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a non-human organism comprising a genetically modified immunoglobulin variable region gene locus produced by the method of replacing, in whole or in part, in an isolated non-human eukaryotic cells, an endogenous immunoglobulin variable region gene locus with an homologous or orthologous human immunoglobulin variable gene locus.

The invention featured a transgenic non-human organism comprising a genetically modified endogenous gene or chromosomal locus. See pages 7-8 of the

specification. The specification discussed the invention as further featuring a transgenic non-human organism whose genome comprises a human variable immunoglobulin gene locus, wherein the human gene locus has replaced the homologous endogenous variable immunoglobulin gene locus. For example, see page 10 of the specification. While the specification has provided extensive guidance pertaining to replacement of an endogenous variable immunoglobulin gene locus in mouse embryonic stem (ES) cells with a corresponding human gene locus, the specification has failed to provide guidance correlating to creation of any transgenic non-human organism whose genome comprises a human variable immunoglobulin gene locus, wherein the human gene locus has replaced the homologous endogenous variable immunoglobulin gene locus. The specification has failed to provide working examples correlating to creation of such a transgenic non-human organism. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, claims 35-39 embrace transgenic non-human organisms comprising a genetically modified immunoglobulin variable region gene locus produced by the method of replacing in whole or in part, in an isolated non-human eukaryotic cell, an endogenous immunoglobulin variable region gene locus with an homologous or orthologous human immunoglobulin variable gene locus. As written, the claims are interpreted to read on replacing immunoglobulin variable region gene locus in an embryonic stem cell, which is subsequently used to create the organism. The following

aspect of the enablement rejection is directed to use of ES cells to make transgenic non-human organisms and germline transmission of ES cells.

Both the specification and the state of the art have taught that transgenic knock-in (replacement of endogenous sequences with exogenous sequences) technology requires the use of embryonic stem cells that have been genetically manipulated. The specification has provided working examples correlating to the use of mouse embryonic stem cells. However, the specification has not provided guidance or working examples correlating to use of non-mouse ES cells (for creation of non-human organisms). Moreover, the specification has not provided guidance correlating to use of an ES cell from a particular species for creation of a transgenic non-human organism from a different species.

With regard to the claim breadth directed to use of non-human eukaryotic cells [see claim 35-38], the specification has failed to provide guidance correlating to use of ES cells, other than mouse. The term "non-human eukaryotic cell " as recited in claim 35 broadly encompasses all non-human eukaryotic cell types. However, as previously discussed the claims are interpreted to read on use of ES cells, given the discussion of the specification (see at pages 7 and 8 for example) for creating transgenic non-human organisms. Presently, ES cell technology is limited to the mouse system as only mouse ES cells achieve germline transmission of a genetic modification. See Hochepied et al (Stem Cells, 2004, 22: 441-447) in the abstract, which reports "Transmission of the genotype to the offspring of chimeras has only been achieved with *M. musculus* ES cells, limiting targeted mutagenesis using ES cells to this species". Although

transmission of ES-cell derived genome to the germ cells and further to the offspring has proved impossible in species other than the house mouse *M. musculus*, Hochepied et al has further reported that "even within *M. musculus* species certain genetic backgrounds have been reported to be less permissive or even non-permissive for germline –competent ES cell derivation. See the first paragraph, in the second column of page 444. Schoonjans et al (Stem Cells, 2003, 21: 90-97) supports the findings of Hochepied by observing that efficiency of derivation of germline-competent ES cell lines from inbred mouse strains, with specific genetic backgrounds, is greatly strain dependent. See page 90 of Schoonjans, in the introduction. Given the state of the art it would appear that germline transmission of a genetic modification is undeveloped and unpredictable in species other than mouse as well as within the various strains of inbred mice. In addition, claims 37-38 read on use of non-mouse ES cells for the production of a transgenic mouse. Neither the specification nor the state of the art has provided guidance relating to production of a transgenic mouse through the use of non-mouse ES cells. Furthermore, claim 39 reads on use of a mouse embryonic stem cell for creating any transgenic non-human organism. Accordingly, with regard to claims 35-38 the specification has failed to provide guidance correlating to the use of ES cells from organisms, other than mouse. Accordingly, given the undeveloped state of the art with respect to availability of ES cells from species other than mouse, it would have required undue experimentation for one skilled in the art to make and use the invention as claimed without a reasonable expectation of success.

As a second issue, claims 35-39 and 46 as written do not convey germline transmission of human immunoglobulin variable region gene loci. The claims merely require a transgenic non-human organism, particularly a mouse, comprising or containing a human immunoglobulin variable region gene locus, wherein the human gene locus may be interpreted to be present in only one cell of the mouse, which may or may not be transmitted through the germline. Moreover, if the human gene locus were expressed in only one cell, then it would be unpredictable if the immunoglobulin variable regions would be expressed at useful levels. The claims as such are not enabled for germline transmission of the human gene locus. Given the lack of guidance provided by the specification it would have required undue experimentation for the skilled artisan to make and use the claimed invention without a reasonable expectation of success.

As a final issue, the claims embrace non-human organisms, particularly mice, comprising a human immunoglobulin variable region gene locus. The guidance provided by the specification correlated to production of a mouse embryonic stem cell comprising a human immunoglobulin variable region gene locus. However, the guidance provided by the specification failed to correlate with production of a single non-human organism embraced by the claims. Moreover, the specification further failed to provide relevant teachings or working examples that correlated to production of any of the non-human organisms embraced by the claims. Although a mouse embryonic stem cell comprising a human immunoglobulin variable region gene locus was made, the mouse stem cell was not actually used to create a transgenic mouse given the prophetic teachings provided by the specification. Given the lack of guidance provided

by the specification it would be unpredictable if such a transgenic non-human organism, particularly a mouse could be made such that human immunoglobulin variable regions would be expressed at a useful level. Furthermore, the specification has also failed to provide any data correlating to levels of human immunoglobulin variable regions produced *in vitro* by any eukaryotic cell. In light of the above, it appears that one of skill in the art could not predict if human immunoglobulin variable regions would be expressed at a useful level correlating to production of human/mouse chimeric antibodies at a useful level. Finally, it is noted that claims 35-39 and 46-47 do not require production of functional antibodies by the non-human organisms, particularly mice, embraced by the claims. The specification has failed to provide guidance with respect to enabled uses other than production of chimeric antibodies as discussed in the specification. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the claimed invention without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the creation of non-human organisms by way of ES cell technology, the lack of direction or guidance provided by the specification correlating to use of ES cells from species other than mouse, the absence of working examples for the demonstration or correlation to creation of non-human organisms comprising human immunoglobulin variable gene regions, the unpredictable state of the art with respect to creation of transgenic non-human organisms, the undeveloped state of the art pertaining to use of ES cells from species other than mouse, it would have required

undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44 and 45 embrace human heavy and light chain immunoglobulin variable region gene loci operably linked to endogenous mouse immunoglobulin constant region gene loci. The claims are indefinite as written because the term "operably linked" implies that (transcriptional) activity of the gene loci is linked. The term operably linked is commonly used when refers to the linkage between a promoter and a gene as the promoter directs transcription of the gene. Accordingly, the context in which gene loci are operably linked is not readily apparent. Appropriate correction is required. Claim 47 depends from claims 44 and 45.

Claim 46 embraces an endogenous immunoglobulin variable region gene locus that has been replaced with a homologous or orthologous human variable region gene locus. The claim is indefinite because it embraces a transgenic mouse containing an endogenous gene locus that has been replaced with an exogenous gene locus. If the

endogenous gene locus was replaced, the transgenic mouse can no longer contain it. Moreover, if the endogenous gene locus was replaced it can no longer be considered endogenous. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 35-39 and 44-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Jakobovits et al (US 6,130,364)

The claims are directed to a non-human organism, particularly a mouse, comprising a genetically modified immunoglobulin variable region gene locus, wherein the endogenous variable immunoglobulin region gene locus has been replaced in whole or in part with a human homologous or orthologous immunoglobulin variable gene locus. The claims are further directed to a transgenic mouse that produces chimeric antibodies comprising human variable regions and mouse constant regions. Claims 35-39 and 46-47 are product by process claims. The method by which the transgenic organisms, particularly mice, were made carries little patentable weight. "[E]ven though

product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Moreover, claims 35-39 and 46-47 as written do not provide a nexus between the modified cells and the organism, particularly a mouse. Accordingly, any transgenic organism, particularly a mouse, comprising a human immunoglobulin variable region gene locus would anticipate the claims.

Jakobovits et al (US 6,130,364) taught the creation of a transgenic mouse comprising a genetically modified immunoglobulin variable region gene locus, which comprises human immunoglobulin variable region light and/or heavy gene loci. At column 6, in lines 34-49, Jakobovits et al discussed that a sequence used for modifying the immunoglobulin gene loci, otherwise known as the modifying sequence, comprises a nucleotide sequence that encodes a translation product to replace all or a portion of either the constant region or the variable regions of an antibody molecule to form a modified antibody molecule. This is interpreted to anticipate limitations in claims 44-45 directed to "human heavy and/or light chain immunoglobulin variable gene loci operably linked to entirely endogenous mouse immunoglobulin constant region gene loci", particularly when taken with the discussions below. Jakobovits et al further discussed that modifying sequences can be used to introduce functional a human heavy or light chain functional immunoglobulin gene locus into an embryonic stem (ES) cell,

particularly a mouse ES cell, which can be used to create a transgenic mouse. See column 7, at lines 36-55. Also, see Jakobovits et al at column 8, at lines 17-65, column 9 at lines 13-15, and column 10 at lines 3-6 directed to immunoglobulin gene loci and modifying sequences and embryonic stem cells. At columns 1 and 8, Jakobovits et al discussed basic antibody structure and immunoglobulin gene loci, such that it is understood that light chains comprise kappa or lamda chains with variable regions and that heavy chains comprise constant and variable regions. Finally, it would appear that the structures of the mouse of Jakobovits et al and the claimed mouse are the same. Therefore, it is inherent that the mouse of Jakobovits et al would produce functional chimeric antibodies in serum, wherein the chimeric antibodies comprise a human variable region and a mouse constant region. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. In any event, it is noted that claims 35-39 and 46-47 do not require production of antibodies by the embraced transgenic non-human organisms, particularly a mouse.

Thus, the teachings of Jakobovits et al anticipated all of the instant claim limitations.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Paras, Jr. whose telephone number is 571-272-4517. The examiner can normally be reached on M-Th, 7-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

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PETER PARAS, JR.
PRIMARY EXAMINER